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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,409	09/26/2006	Atanas Iliev Lalev	13993-4	7611

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EXAMINER	
YAKOVLEVA, GALINA M	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/568,409	LALEV ET AL.
	Examiner	Art Unit
	GALINA YAKOVLEVA	1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 June 2011 and 14 March 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26,29-32 and 34-52* is/are pending in the application.

4a) Of the above claim(s) *29-31,36,41-44 and 47-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26,32,34,35,37-40,45 and 46* is/are rejected.

7)☒ Claim(s) *5,8-21,25,32,37,39,40,45 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Responsive to communications entered 06/08/2011 and 03/14/2011.

Status of Claims

Claims 1-26, 29-32 and 34-52 are pending. Claims 27, 28 and 33 are cancelled. Claims 29-31, 36, 41-44 and 47-52 are withdrawn as being directed to non-elected species per restriction requirement mailed 04/02/2009. Claims 1-26, 32, 34, 35, 37-40, 45 and 46 are examined.

No effect was given to Applicant's attempt to withdraw Claims 5, 10-21, 25, 32, 37, 39, 40, 45 and 46 from prosecution because no authority in support of applicant's power to withdraw claims from prosecution was found.

Priority

The instant application, Pub. No. US 2007/0148715-A1, is a 371 filing of PCT/CA04/01448 filed 07/30/2004, which claims benefit of 60/494,811 filed 08/14/2003 and claims benefit of 60/545,493 filed 02/19/2004 and claims benefit of 60/566,396 filed 04/30/2004.

Withdrawn Objections/Rejections

I. The objection to Claims 36, 48 and 49 is withdrawn in view of Applicant's correction of the status identifier.

II. The rejection Claims 1-2, 5-6, 8-9, 22-23, 25, 26, 32, 34-35 and 38-40 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Publication No. 2004/0142488 to Gierde *et al.* ("Gierde") in view of U.S. Patent No. 7,379,820 to Sukits *et al.* ("Sukits") is withdrawn in view of Applicant's argument.

III. The rejection Claims 3, 4 and 10-21 under 35 U.S.C. 103(a) as being unpatentable over Rigaut *et al.*, Nature Biotechnology (1999) 17:1030-1032 in view of U.S. Patent Publication No. 2004/0142488 to Gierde *et al.* ("Gierde") and U.S. Patent No. 7,379,820 to Sukits *et al.* ("Sukits") is withdrawn in view of Applicant's argument.

IV. The rejection of Claim 7 under 35 U.S.C. 103(a) as being unpatentable over Gierde in view of Sukits as applied to claims 2 and 6, and further in view of Rigaut is withdrawn in view of Applicant's argument.

V. The rejection of Claim 24 under 35 U.S.C. 103(a) as being unpatentable over Gierde in view of Sukits as applied to claims 1 and 22-23 and further in view of U.S. Patent No. 5,007,934 to Stone and U.S. Patent No. 5,849,885 to Nuyens *et al.*, is withdrawn in view of Applicant's argument.

VI. The rejection Claims 45 and 46 under 35 U.S.C. 103(a) as being unpatentable over under 35 U.S.C. 103(a) as being unpatentable over Gierde in view of Sukits as applied to claim 1 above, and further in view of U.S. Patent 6,610,508 to Hentze *et al.* ("Hentze") and evidenced by U.S. Patent No. 5,753,225 to Clary *et al.* is withdrawn in view of Applicant's argument.

Claim Objections

Claims 5, 8-21, 25, 32, 37, 39-40 and 45-46 are objected to because of the following informalities: the claims have an incorrect status identifier. In the Reply to Notice of Non-Compliant Amendment, which Reply was entered 06/08/2011, Claims 5, 8-21, 25, 32, 37, 39-40 and 45-46 were identified as "Withdrawn." However, Claims 5, 8-21, 25, 32, 37, 39-40 and 45-46 are pending. Appropriate correction is required.

Claims 29-31 and 47 are objected to because of the following informalities: the claim has an incorrect status identifier. Since the claim is withdrawn as being directed to non-elected species, it should be identified as "Withdrawn." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23-26, 34, 45 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to Claims 23-26, it is not clear how “the ionic strength of the system is increased with a chemical agent.” It appears that wording “concentration of” is missing.

With regard to Claims 25, 26 and 34, recitation “the change of the concentration” lacks proper antecedent basis. Furthermore, this recitation is unclear. Does it mean “a gradient of the concentration?”

With regard to Claims 45 and 46, it is not clear how “a method of separating a first ligand from a second ligand in an affinity matrix system” provides for ligand- ligand association as a putative cause for a disease to be identified.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 25, 26 and 34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the following aspects of the claimed invention have not been described with sufficient particularity such that one skilled in the art would recognize that the applicant had possession of the claimed invention:

Claim 25 - “the change of the concentration of the chemical agent is less than 30 mM;”

Claim 26 – “the change of the concentration of the chemical agent is between 30 mM and 2M;”

Claim 34 – “the change of the concentration of the chemical or biomolecule is below 30 mM.”

In fact, these limitations are in contradiction to Applicant’s own terminology, which defines the concentration of the chemical agent to be at least 100 mM:

[0144] The term "removing unbound substances from the affinity matrix" as used herein means washing the affinity matrix with the immobilized second ligand bound in a manner that removes unbound substances from the affinity matrix while leaving the immobilized second ligand bound to the affinity matrix and the first ligand still associated with the second ligand. In one example, the wash buffer is *100 mM KCl*, 10 mM HEPES pH 7.4, 5% glycerol, 1% DMSO, 0.1% TritonX100.

[0145] The term "separating the first ligand from the immobilized second ligand" as used herein means separating the first ligand from the immobilized second ligand in a manner that removes the first ligand from the second ligand while leaving the immobilized second ligand bound to the affinity matrix. The first ligand can be separated from the immobilized second ligand by disrupting the electrostatic forces between the first ligand and the immobilized second ligand. The electrostatic forces can be disrupted by using an elution buffer that increases the ionic strength of the medium. In one example, the ionic strength of the medium is increased using an elution buffer with an increased salt concentration, such as *0.3-0.5M potassium chloride* (KCl) or *0.7M potassium acetate*. The instant application, Pub. No. US 2007/0148715-A1; Emphasis added.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-26, 32, 34, 35, 37-40, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Seraphin** *et al.*, U.S. 2002/0061513, published 05/23/2002, as evidenced by **Fink** *et al.*, "Classification of Acid Denaturation of Proteins: Intermediates and Unfolded States," *Biochemistry*, 1994, *33* (41), pp. 12504–12511, in view of **Kellogg** *et al.*, "Protein- and immunoaffinity purification of multiprotein

complexes," *Methods in Enzymology*, 2002, vol. 351, pp. 172–183 and **Hentze** *et al.*, U.S. Patent 6,610,508, issued 08/26/2003 (of record); PCT counterpart of Hentze *et al.*, WO 2000/053779, published 09/14/2000.

Seraphin *et al.*, throughout the publication, and, for example, in paragraphs [0015]-[0018] teach a method for detecting and/or purifying protein or biomolecule complexes, which method comprises the steps:

(a) providing an expression environment containing one or more heterologous nucleic acids encoding at least two subunits of a biomolecule complex, each being fused to at least one of different affinity tags, one of which consists of one or more IgG binding domains of Staphylococcus protein A,

(b) maintaining the expression environment under conditions that facilitate expression of the one or more subunits in a native form as fusion proteins with the affinity tags, and under conditions that allow the formation of a complex between the one or more subunits and possibly other components capable of complexing with the one or more subunits,

(c) detecting and/or purifying the complex by a combination of at least two different affinity purification steps each comprising binding the one or more subunits via one affinity tag to a support material capable of selectively binding one of the affinity tags and separating the complex from the support material after substances not bound to the support material have been removed.

In paragraph [0028], Seraphin *et al.* teach the use of affinity chromatography on affinity columns which contain a matrix coated with the appropriate binding partner for the affinity tag used in the particular purification step. In paragraph [0044], Seraphin *et al.* teach that any conventional affinity tags, in addition to the IgG binding domains, can be used, and, preferably, the second affinity tag consists of at least one calmodulin binding peptide (CBP). In paragraph [0029], Seraphin *et al.* teach two affinity steps to be carried out, wherein each affinity step consists of a binding step in which the previously extracted protein is bound via one of its affinity tags to a support material which is covered with the appropriate binding partner for that affinity tag; then unbound substances are removed and finally the protein to be purified is recovered from the support material. In paragraph [0031], Seraphin *et al.* teach that a specific proteolytic cleavage site is present in the fusion protein between the one or more polypeptides or subunits and the one or more affinity tags so that proteolytic cleavage allows the removal of at least one of the affinity tags, especially the IgG binding domains of protein A. In paragraph [0032], Seraphin *et al.* teach that proteolytic cleavage can be carried out by chemical means or enzymatically. In paragraph [0033], Seraphin *et al.* teach an enzymatic cleavage by the TEV protease to remove the protein A domains from the fusion protein. In paragraph [0037], Seraphin *et al.* teach that the method not only facilitates efficient purification of proteins of interest but also allows fishing for and detecting components present in complexes with which the polypeptides or subunits are associated or complexed either directly or indirectly, e.g. molecules such as linker mediators, and this would allow selective fishing for certain substances which may be

potential drugs even from complex mixtures. In paragraph [0038], Seraphin *et al*. teach that it is possible not only to detect or purify the subunit containing fusion proteins expressed but also other substances that are capable of associating with the proteins expressed in a direct way, i.e. by directly binding to the fusion protein, or indirectly via other molecules to form biomolecule complexes. In paragraph [0038], Seraphin *et al*. teach that, if a fusion protein of a subunit of a biomolecule or protein complex is purified, the affinity steps are chosen so that other complex components which have bound to the fusion protein are still associated with the subunit after the purification steps so that they can be detected/purified as well. In paragraph [0039], Seraphin *et al*. teach that the biomolecule complexes can be formed in the expression environment such as cellular complexes. In paragraph [0040], Seraphin *et al*. teach the expression of two (or more) subunits of the same complex each as a fusion protein with a different affinity tag; when the subunits associate they can be detected/purified possibly together with other complex components by a series of affinity steps in which each time the complex is bound via a differently tagged subunit; the two or more affinity tags can be fused with a single subunit of a complex or with two or more subunits which bind to each other or are simply present in the same complex. In paragraph [0043], Seraphin *et al*. teach fusing a subunit of to one tag and fusing another subunit with a different tag. In paragraph [0024], Seraphin *et al*. teach the fusion proteins containing mutation(s). In paragraph [0029], Seraphin *et al*. teach the use of conventional elution techniques such as varying the pH or the salt or buffer concentrations for recovering the protein from the support material. Seraphin *et al*. do not expressly teach separating the first ligand from the

immobilized second ligand, which remains bound to the affinity matrix during the separation, by decreasing the electrostatic forces between the first ligand and the second ligand. Nevertheless, the elution techniques, taught by Seraphin *et al.*, such as varying the salt concentrations, as evidenced by **Kellogg** *et al.* and **Fink** *et al.,* discussed below, shall inevitably lead to disrupting the proteins associated *in vivo* by the electrostatic forces.

Seraphin *et al.* do not teach that "the change of the concentration of the chemical agent is between 30 mM and 2M."

Kellogg *et al.*, throughout the publication, and, for example, at page 179, teach purification of endogenous multiprotein complexes by immunoaffinity chromatography. At page 179, second paragraph, Kellogg *et al.* teach the associated proteins to be eluted with a high salt buffer, leaving the original protein still bound to the antibody on the column. At page 183, last paragraph, Kellogg *et al.* teach that protein interactions that can only be disrupted with high salt (e.g., >0.5 M) are most likely to interact *in vivo*. At page 178, fourth paragraph, Kellogg *et al.* teach the use of a salt gradient going from 0.3 to 1.0 M KCl. Although Kellogg *et al.* do not teach "the change of the concentration of the chemical agent is between 30 mM and 2M," it would have been obvious to one of ordinary skill in the art to select a change in concentration using the ranges claimed. Indeed, the skilled artisan would have arrived at the claimed ranges based on the doctrine of routine optimization. In a case decided by the precursor to the Federal Circuit, the court stated that a claim is not allowable where the skilled artisan could have arrived at the claim through routine experimentation on the optimum or workable ranges

of the claim. *In re Aller*, 220 F.2d 454, 456 (CCPA 1955) (stating "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."). MPEP 2144.05.

Although Kellogg *et al.* do not specify the nature of the forces, by which the proteins associated *in vivo,* one of ordinary skill in the art would have known that the salt elution disrupts the proteins associated by the electrostatic forces, because, as evidenced by **Fink** *et al.,* it is the well-known fact that salts (anions) affect the electrostatic interactions in proteins (see, for example, Abstract of the Fink *et al.* reference).

It would have been *prima facie* obvious, at the time the invention was made, for one of ordinary skill in the art to have made and used the salt gradient, taught by Kellogg *et al.*, in a method, taught by Seraphin *et al.*

One of ordinary skill in the art would have been motivated to have made and used the salt gradient, taught by Kellogg *et al.*, in a method, taught by Seraphin *et al.*, because it would be desirable to separate the proteins associated *in vivo* by the electrostatic forces.

One of ordinary skill in the art would have had a reasonable expectation of success in making and using the salt gradient, taught by Kellogg *et al.*, in a method, taught by Seraphin *et al.*, because protein-protein interaction is a type of ligand-ligand interaction, which is known to be disrupted by the salt gradient, as taught by Kellogg *et al.*

Neither Seraphin *et al.* nor Kellogg *et al.* teach a method of separating a first ligand from a second ligand in an affinity matrix system, wherein ligand-ligand association as a putative cause for a disease is identified.

Hentze *et al.*, throughout the publication, and, for example, at column 1, lines 33-54; column 30, lines 58-62, teach a step of identifying protein-protein interactions in order to detect disease states, including Alzheimer's disease.

With the foregoing description in mind, one of ordinary skill in the art would have found it obvious to modify the Seraphin *et al.*'s method to include the step of identifying protein-protein interactions for detecting Alzheimer's disease. The skilled artisan would have made the modification because detecting Alzheimer's disease informs a patient whether the disease state is present.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GALINA YAKOVLEVA whose telephone number is (571)270-3282. The examiner can normally be reached on Monday-Friday 8:00 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on (571)272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G. Y./
Examiner, Art Unit 1641

/SHAFIQUL HAQ/
Primary Examiner, Art Unit 1641